REMARKS

The Office Action dated May 13, 2008 has been carefully reviewed and the foregoing amendments are made in response thereto. In view of the above amendments and following remarks, Applicants respectfully request reconsideration of this application and timely allowance of the pending claims.

By this paper, claim 53 has been amended to incorporate the features of claim 64. Furthermore, claim 66 has been amended to incorporate the features of claim 78. In addition, claims 64 and 78 have been canceled to avoid potential redundancy. Since the amendment merely rewords the language of existing claims, no prohibited new matter is introduced to the original disclosure.

Upon entry of this amendment, claims 53 to 63 and 65 to 77 will be pending.

Summary of the Office Action of May 13, 2008

1. The Examiner requests applicants to submit copies of the non-U.S. patent and literature references cited in the Information Disclosure Statement ("IDS") filed on January 23, 2008.

2. Claims 53 and 61 to 63 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Mizuno et al.

3. Claims 54 to 60, 64 to 78, and 87 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Mizuno et al and further in view of Sah et al, Langer et al., and Anseth et al.

IDS References

Applicants respectfully note the present application does not claim priority under 35 U.S.C. § 120 to the U.S. Application No. 10/681,752.

Applicants are now in the process of submitting copies of the non-U.S. patent and literature references cited in the Information Disclosure Statement ("IDS") filed on January 23, 2008.

Claim Rejections under 35 U.S.C. § 103(a)

Claims 53 and 61 to 63 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Mizuno et al. Claims 54 to 60, 64 to 78, and 87 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Mizuno et al and further in view of Sah et al., Langer et al., and Anseth et al.

Applicants respectfully disagree with the Examiner for the reasons set forth below.

Establishing *prima facie* obviousness requires a showing that the prior art references, when combined, teach or suggest all the claim limitations. Furthermore, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Recently, the United States Supreme Court also expressed the need to an "explicit" showing of "some apparent reason to combine the known elements in the fashion claimed by the patent at issue" and that "rejection on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, slip op. at 14 (2007).

Applicants respectfully submit that the claimed invention, as amended, is not rendered obvious by the cited references because the cited references, taken alone or in combination, do not teach or suggest the claimed limitations of the present invention. Furthermore, there is no disclosure or suggestion provided in the cited references, or otherwise of the record, which would motivate one skilled in the art to modify the methods of the cited references in such a way to arrive at the claimed invention.

The claimed invention is directed to a method of producing a multi-layered tissue construct *in vivo* which includes, *inter alia*, the step of additionally crosslinking the first and second polymerizable mixtures until the first and second layers further polymerize to form an integrated multi-layered gel. For example, each of the three Illustrative Examples of the present application (pages 58 to 67) includes the step of additionally exposing the multiple polymer layers to UV radiation to complete the integration of these layers.

Mizuno et al. relate to specific methods for preparing tissue constructs that include an integration layer and a cell-seeded support matrix. Mizuno et al. also contemplate a protective layer. However, Mizuno et al. do not disclose or remotely suggest a step of additionally crosslinking the multiple layers to form an integrated multi-layered gel. In other words, the multiple layers in the Mizuno tissue construct are individual layers stacked together, while the multiple layers of the present invention are individual layers formed into a whole, i.e., integrated.

More importantly, the present integrated multi-layered tissue construct has unexpected and superior properties. Specifically, according to Table 1 of Illustrative Example 2 (pages 61 to 64), the measured shear modulus and Young's modulus for the two-layered integrated tissue construct (S/D) was significantly greater than any of the mono-layered tissue construct. In other words, the two-layered integrated tissue construct was stronger and had greater shear and peel strength characteristics than the mono-layered tissue constructs, let alone a multi-layered construct wherein the multiple layers are stacked together, such as the Mizuno construct.

Furthermore, the first polymerizable mixture of the present invention contains first cells and is placed in an osteochondral tissue space, while Mizuno et al. fail to disclose or suggest placing the first polymer layer having first cells in an osteochondral tissue space.

Mizuno et al. disclose that the integration layer is in direct contact with an organ or tissue as an interface between a later-applied cell-seeded support matrix and the native organ or tissue. (See column 12, lines 12 to 20) Thus, in the Mizuno composition, the integration layer is the first layer and in direct contact with an tissue, while the cell-seeded support matrix is the second layer and is insulated from other cells by the integration layer.

Particularly, in the circumstances where the multi-layered composition is applied to an osteochondral tissue place, Mizuno et al. emphasize that the layer in direct contact with the osteochondral tissue does not contain any cells and even prevents infiltration of cells from the bone tissue underneath. For example, Mizuno et al. state:

> "In one embodiment, the integration layer prevents the infiltration of blood vessels and unwanted cells from underlying bone tissue into a chondrocyte seeded matrix implanted into an articulating joint of a host."
> (Column 12, lines 32-37, underline added)

Thus, when the Mizuno composition is applied to a bone tissue place, the integration layer needs to shield the cell-seeded second layer from other cells, let alone contains any cells in itself.

Mizuno et al. also contemplate a protective layer, which "encapsulates the outer surface of a cell seeded support matrix." (See column 13, lines 29 to 30) In other words, when a protective layer is applied, the cell seeded support matrix is not in directed contact with a tissue. Below is a preferred example of Mizuno et al. wherein a protective layer is placed in a bone tissue place:

> "In a preferred embodiment, the protective layer comprises a proprietary solution, designated CT3, ... a surgeon applies this aerosolized CT3 to subchondral bone in situ. In placing the cellular support layer, a surgeon places the polymer material in the lesion and, without waiting for it to fully polymerize, places the neo-cartilage into position. In this way, the layer facing subchondral bone seals-off the subchondral bone and holds the cellular support layer (e.g. neo-cartilage) in place. The outer protective layer ... is applied in such a manner as to keep it below the articulating surface of the joint to prevent it from being displaced by friction." (Column 13, lines 38-53, underline added)

The protective layer described above serves as the first layer and is in direct contact with the subchondral bone tissue. The above process clearly indicates that the protective layer, i.e., the first layer, does not contain any cells and insulates the cell-seeded second layer from the subchondral bone tissue.

In view of the foregoing, Mizuno et al. repeatedly teach that the cell-seeded layer of a multi-layered tissue construct is not in direct contact with osteochondral tissue.

It is true that Mizuno et al. contemplate placing a fibrolasts-seeded integration layer to a skin tissue place, but Mizuno et al. also specifically and repeatedly emphasize that the layer in direct contact with the osteochondral tissue does not contain any cells and even prevents infiltration of cells from the bone tissue underneath, as discussed above. Applicants respectfully submit that one skilled in the art, in view of Mizuno et al., would not be motivated to place the first polymer layer having first cells in an osteochondral tissue space since Mizuno et al. specifically and repeatedly teach against such a modification.

Therefore, the claimed method is not rendered obvious by the disclosure of Mizuno et al.

Inasmuch as the principle reference, Mizuno et al., does not teach or suggest the claimed limitations of the present invention, the other applied references, namely, Langer et al., Anseth et al., and Sah et al. are further removed from the claimed method since none of them cure the defect of Mizuno et al. Specifically, Langer et al. disclose compositions for tissue engineering using photocrosslinkable polymeric hydrogels, Anseth et al. investigate photoinitiated polymerizations in tissue engineering, and Sah et al. is directed to a cultured, stratified cartilage tissue construct and a method of making the same. However, none of Langer et al., Anseth et al., and Sah et al. disclose or remotely suggest the step of additionally crosslinking the first and second polymerizable mixtures until the first and second layers further polymerize to form an integrated multi-layered gel. Thus, combination of the cited references does not teach or suggest the present method.

The § 103 rejections also fail because there is no motivation in the applied references or in the general knowledge of one skilled in the art which suggest modifying the disclosed methods to include Applicants' claimed step of additionally crosslinking the multiple layers to form an integrated multi-layered gel. Thus, there is no motivation provided in the applied references, or otherwise of record, to make modifications to arrive at the claimed invention.

Therefore, the claimed invention, as amended, is not rendered obvious by the cited references.

In view of the foregoing, one skilled in the art would not be motivated to combine the methods disclosed by the cited references in the fashion claimed by the present application. Therefore, Applicants respectfully request that the rejections under 35 U.S.C. § 103 be withdrawn.

Conclusions

In view of the foregoing, it is believed that each ground of rejections set forth in the Office Action has been overcome. Thus, favorable reconsideration and allowance is respectfully solicited.

Except for issues payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a constructive petition for extension of time in accordance with 37 C.F.R. 1.136(a)(3).

Should the Examiner have any remaining questions, she is invited to telephone the undersigned.

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Respectfully submitted,
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